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isoindol-2-yl)-piperidine-2,6-dione which occurred in the prior cycle by Day 42 or sooner (28-day cycle plus limit of 2 weeks to recover) as evidenced by a return to Grade ≤ 1 toxicity level. Patients who experience DLT in the previous cycle should have their dose modified. DLT is defined as an non-hematological event Grade ≥ 3 toxicity or hematological event of Grade 4 toxicity thought to be related to the study medication. Patients who experience DLT in the first cycle and have no response to therapy are removed from the study.

3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione doses are subsequently escalated to 5, 8, 11, 15, and 20 mg/m²/day to a maximum total daily dose of 40 mg. Patients continue to receive 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione on a 4-week cycle per dose level until one of the off-study criteria are met.

Three patients are enrolled in each cohort. If at least one DLT occurs, three additional patients are added to the cohort at that particular dose level. If two DLTs occur, the MTD, defined as the dose at which fewer than one-third of patients at each dose level experiences DLT has been exceeded and four more patients are treated at the previous dose.

Patients who experience DLT during the first 4-week cycle are removed from the study, except if they have a response to therapy. For patients who have completed their first 4-week cycle of without DLT, but who subsequently experience Grade 3 or 4 hematological and/or nonhematological toxicity, treatment is suspended for a minimum of a week. If the toxicity resolves to <Grade 2 within three weeks, the patient is treated at two dose levels lower than the dose that caused the toxicity (or a 50% reduction if the patient was treated at the first or second dose level). Patients in whom Grade 3 or 4 toxicity does not resolve to <Grade 1 within three weeks, or those who have another Grade 3 toxicity at the reduced dose are removed from the study.

Pharmacokinetic sampling is performed prior the first dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Day 1) and 0.5, 1, 2, 4, 6, 8, 24, and 48 hours thereafter. Sampling is also conducted pre-dose on Days 7 and 21 and 0.5, 1, 2, 4, 6, 8, and 24 post-dose on Day 21 to evaluate steady-state 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione levels.

6.5.5 Treatment of Metastatic Melanoma

Patients with metastatic melanoma were started on 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revmid™) at 5 mg/day for seven days. The dose was then increased every seven days to 10 mg/day, 25 mg/day, and 50 mg/day, respectively, for a total of four weeks on therapy. Five of the 13 melanoma patients who were treated under this regimen either showed disease stabilization or a partial response in the first four weeks of treatment. Tumor response was seen in cutaneous and subcutaneous lesions (five patients), lymph nodes (two patients), and liver (one patient). The duration of response was approximately six months. The result suggests that the compound appears is a promising new anti-cancer agent and has both antiangiogenic and immunomodulatory properties.

6.5.6 Treatment of Relapsed or Refractory Multiple Myeloma

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks. Maintenance treatment consisting of daily an immunomodulatory compound of

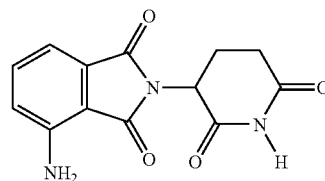
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the invention and monthly dexamethasone are continued until the disease progression. The therapy using an immunomodulatory compound of the invention in combination with melphalan and dexamethasone is highly active and generally tolerated in heavily pretreated multiple myeloma patients whose prognosis is otherwise poor.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

What is claimed is:

1. A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma: (a) from about 1 mg to about 5 mg per day of a compound having the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle, and (b) 40 mg of dexamethasone.

2. The method of claim 1, wherein the multiple myeloma is relapsed and refractory multiple myeloma.

3. The method of claim 1, wherein the multiple myeloma is newly diagnosed multiple myeloma.

4. The method of claim 1, wherein the multiple myeloma is refractory multiple myeloma.

5. The method of claim 1, wherein the multiple myeloma is relapsed multiple myeloma.

6. The method of claim 1, wherein the patient has received previous therapy.

7. The method of claim 1, wherein the patient has demonstrated disease progression on previous therapy.

8. The method of claim 1, wherein the patient has received previous therapy and has demonstrated disease progression on previous therapy.

9. The method of claim 6, wherein the previous therapy is treatment with thalidomide, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a proteasome inhibitor, stem cell transplantation, or a combination thereof.

10. The method of claim 1, wherein the compound is administered in an amount of about 4 mg per day.

11. The method of claim 1, wherein the compound is administered in an amount of about 3 mg per day.

12. The method of claim 1, wherein the compound is administered in an amount of about 2 mg per day.

13. The method of claim 1, wherein the compound is administered in an amount of about 1 mg per day.

14. The method of claim 1, wherein the dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15 and 22 of each 28 day cycle.

15. The method of claim 1, wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle.